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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,192	07/14/1999	ALAN GEORGE BAXTER	229752000600	5844

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/308,192	Baxter
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 9, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19 and 22* is/are pending in the application.

4a) Of the above, claim(s) *5, 6, 11-19, and 22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4 and 7-10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *16*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicant's submission filed on 12/09/02 (paper no. 21) has been entered.

Applicant's Amendment

2) Acknowledgment is made of Applicant's amendment filed 11/08/02 (paper no. 18) in response to the final Office Action mailed 06/10/02 (paper no. 15).

Status of Claims

3) Claim 1 has been amended via the amendment filed 11/08/02.

Claims 1-19 and 22 are pending.

Claims 1-4 and 7-10 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

6) The rejection of claims 1-4 and 7-10 made in paragraph 8 of the Office Action mailed 06/10/02 (paper no. 15) under 35 U.S.C. 112, first paragraph, as containing new matter, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph

7) Claims 1-4 and 7-10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of immunomodulatory treatment of a mammal with insulin dependent diabetes mellitus (IDDM) comprising administering to said mammal an

immunomodulating effective amount of mycolyl-arabinogalactan-peptidoglycan (MAPG) obtained from an undisclosed species of *Mycobacterium*, does not reasonably provide enablement for a method of immunomodulatory therapy in any mammal, human or non-human, for the treatment of any non-IDDM autoimmune disease comprising administering to said mammal an immunomodulating effective amount of any one or more isolated components of the cell wall of any species of *Mycobacterium*, or the MAPG derived from *M. bovis*, as claimed broadly.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a method of immunomodulatory therapy in a human or non-human mammal for the treatment of an autoimmune disease, such as, IDDM, thyroiditis, type A atrophic gastritis, pernicious anemia, Addison's disease, pemphigus vulgaris, pemphigoid, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, haemolytic anaemia, sympathetic ophthalmia, uveitis, idiopathic thrombocytopenia, idiopathic leucopenia, primary biliary cirrhosis, autoimmune chronic active hepatitis, ulcerative colitis, Sjogren's syndrome, dermatomyositis, scleroderma or mixed connective tissue disease, comprising administering one or more isolated cell wall components of *Mycobacterium*, including the MAPG derived from *M. bovis* or component(s) thereof. Although the relative skill of those in this art is high, the breadth of the claims encompasses the use of any cell wall component of any species of *Mycobacterium* in the method of treatment of any of the above-cited autoimmune diseases. A review of the instant specification shows that one cell wall component, MAPG, obtained from an undisclosed species, when administered to NOD mice showed therapeutic effects against IDDM. See Example 12 and Figure 6. Example 4 describes that MAPG

was obtained from the Tuberculosis Repository, but does not disclose which species of *Mycobacterium* was it obtained from. Other than this MAPG, no other isolated mycobacterial cell components from any species of *Mycobacterium* have been used or administered to a mammal, human or non-human, in a method of immunomodulatory therapy wherein the administered component(s) have shown a significant therapeutic effects against IDDM, or one or more of the autoimmune diseases, such as, IDDM, thyroiditis, type A atrophic gastritis, pernicious anemia, Addison's disease, pemphigus vulgaris, pemphigoid, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, haemolytic anaemia, sympathetic ophthalmia, uveitis, idiopathic thrombocytopenia, idiopathic leucopenia, primary biliary cirrhosis, autoimmune chronic active hepatitis, ulcerative colitis, Sjogren's syndrome, dermatomyositis, scleroderma or mixed connective tissue disease, as currently claimed. On the contrary, Example 11 of the instant specification shows that NOD mice treated with mycobacterial subfractions, GMDP and ManLAM did indeed develop diabetes, instead of getting cured or protected. Furthermore, there is no showing that the components of MAPG, mycolic acid, arabinogalactan and peptidoglycan from one or more species of any *Mycobacterium*, were successfully used in a method of immunomodulatory treatment of even IDDM, let alone other recited autoimmune diseases. Without a concrete showing, there is no predictability that the various MAPG components or MAPG from any species of *Mycobacterium* would indeed elicit immunotherapeutic effects against all the recited autoimmune diseases. A mere mentioning in the specification of a series of autoimmune diseases (see page 6, lines 20-26) is insufficient to enable a method of immunotherapy in human or non-human mammals against all these autoimmune conditions. In fact, the art specifically teaches that the mycolic acid diester isolated from mycobacteria induced most of the undesirable side effects, including adjuvant arthritis and autoimmune diseases. For instance, see fifth full paragraph in column 2 of Berger *et al.* (US 4,877,612).

The applied art (see below) establishes that some cell wall components of some *Mycobacteris* are successfully used to treat autoimmune IDDM. However, with regard to the treatment of any autoimmune disease with any cell wall component(s), including mycolic acids, peptidoglycan, arabinogalactan, components of MAPG and other associated cell wall components, or submolecular components of any species of *Mycobacterium*, the specification is not adequately

enabling. Clearly, the full scope of the claims is not commensurate with the enabling disclosure or evidence. Without isolation of a representative number of specific cell wall components of specific species of *Mycobacterium* followed by their evaluation in human or non-human therapeutic models of IDDM, thyroiditis, type A atrophic gastritis, pernicious anemia, Addison's disease, pemphigus vulgaris, pemphigoid, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, haemolytic anaemia, sympathetic ophthalmia, uveitis, idiopathic thrombocytopenia, idiopathic leucopenia, primary biliary cirrhosis, autoimmune chronic active hepatitis, ulcerative colitis, Sjogren's syndrome, dermatomyositis, scleroderma or mixed connective tissue disease, and without a specific immunotherapeutic demonstration, one of ordinary skill in the art would not be able to practice the full scope of the invention and therefore, and would not be able to reproducibly practice the claimed invention without undue experimentation. Berger's disclosure and Applicants' own results described in Example 11 provide *prima facie* evidence for unpredictability associated with treating an autoimmune disease with any isolated mycobacterial cell wall component. Therefore, given the lack of specific disclosure and/or specific guidance in the specification, the breadth of the claims, quantity of experimentation required and the associated unpredictability, one of ordinary skill in the art could not practice the full scope of the claimed invention, without considerable undue experimentation. The ability to reproducibly practice the full scope of the claimed method is well outside the realm of routine experimentation. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

8) Claims 7-9 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regards as the invention.

(a) Claims 7 and 9 are vague and confusing in the recitation: "a component thereof" or "its components". It is unclear what is encompassed in this limitation. Since the MAPG recited in the claims encompasses or includes an unpurified MAPG, what qualifies as a 'component thereof' or 'its components' is not clear. Is an impurity component associated with MAPG encompassed in the scope of the limitation "component thereof" or "its components".

(b) Claim 8 is confusing and/or incorrect in the recitation "mycolic of acids".

Rejection(s) under 35 U.S.C. § 102

9) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10) Claims 1-3, 7 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stanford *et al.* (WO 85/05034).

Stanford *et al.* disclosed a method of treating autoimmune arthritic conditions, such as, adjuvant arthritis in a mammal and a patient (i.e., inclusive of a human patient) comprising administering a pharmaceutical preparation comprising an acetone soluble fraction of mycobacterial cells (see page 2; page 3, lines 18-22; paragraph bridging pages 4 and 5; Table 4; and claims, especially claim 15). Stanford *et al.* also showed that peripheral blood mononuclear cells of none of seventeen rheumatoid arthritis patients showed proliferative responses to the mycobacterial acetone soluble fraction (see Table 5). That prior art acetone soluble fraction of the mycobacterial cells contains isolated mycobacterial cell wall components or a component of MAPG is inherent from the disclosure of Stanford *et al.* since it is well known in the art that impure mycobacterial cell wall components or impurities are acetone soluble.

Claims 1-3, 7 and 10 are anticipated by Stanford *et al.*

11) Claims 1-4 are rejected under 35 U.S.C. § 102(a) as being anticipated by Stosic-Grujicic *et al.* (*Mikrobiologija* 33 (1): 27-36, 1996).

Stosic-Grujicic *et al.* taught a method of treating autoimmune diabetes in mice by administering 10 or 50 micrograms per injection (i.e., immunomodulating effective amount) of well-defined immunomodulatory mycobacterial components derived from the cell wall, a trehalose dimycolate (TDM) and PPD. Both TDM and PPD emulsified in incomplete Freund's adjuvant (IFA) protected mice from autoimmune diabetes or IDDM. See page 29, second paragraph; page 30, second paragraph; and 'Conclusion'.

Claims 1-4 are anticipated by Stosic-Grujicic *et al.*

Rejection(s) under 35 U.S.C. § 103

12) Claims 1 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stosic-

Grujicic *et al.* (*Mikrobiologija* 33 (1): 27-36, 1996).

The disclosure of Stosic-Grujicic *et al.* is explained above which does not expressly teach their method being used in a human. However, Stosic-Grujicic *et al.* teach that their diabetes animal model is a model system not only to study the pathogenesis of the disease that is similar to human IDDM, but also a means with which to test intervention protocols to be used to prevent the disease in humans (see second paragraph under 'Introduction').

Given that the murine model is generally accepted in the art as predictive of therapeutic efficacy in humans, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use or extend Stosic-Grujicic's method of treating autoimmune diabetes to another mammalian subject, such as a human subject, to produce the method of the instant invention, with a reasonable expectation of success. Since human clinical trials are often conducted following the successful animal experimentation, a skilled artisan would have been motivated to produce the instant invention by extending Stosic-Grujicic's method to humans for the expected benefit of treating IDDM in humans, as treatment of IDDM in humans is generally highly desired in the art.

Claims 1 and 10 are *prima facie* obvious over the prior art of record.

Remarks

13) Claims 1-4 and 7-10 stand rejected.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which receives papers 24 hours a day and seven days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

15) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the

Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

February, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER